Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017;376:125-35. DOI: 10.1056/NEJMoa1607427

^{177}LU-DOTATATE PHASE 3 TRIAL IN MIDGUT NEUROENDOCRINE TUMORS

SUPPLEMENTARY APPENDIX

TABLE OF CONTENTS

Acknowledgements

We thank the participating patients and their families, as well as the global network of research nurses, trial coordinators, and operations staff for their contributions, and the investigators whose patients were enrolled in this trial, including: **Belgium**: Eric Van Cutsem; **France**: Catherine Ansquer, Eric Baudin, Frederic Courbon, Francesco Giammarile, Philippe Ruszniewski, David Taieb; **Germany**: Richard P. Baum, Marianne Pavel, Klemens Scheidhauer, Matthias Weber; **Italy**: Lisa Bodei, Ernesto Brianzoni, Gianfranco Delle Fave, Maria Chiara Grana, Giuliano Mariani, Guido Rindi, Ettore Seregni, Stefano Severi; **Portugal**: Isabel Azevedo; **Spain**: Enrique Grande, Jaime Mora; **Sweden**: Kjell Öberg, Anders Sundin; **United Kingdom**: Adil Al-Nahhas, Martyn Caplin, Nick Freemantle, Ashley Grossman, Prakash Manoharan, Nicholas Reed, Rajaventhan Srirajaskanthan; **USA**: Lowell Anthony, Al B. Benson, Jordan Berlin, David Bushnell, Ebrahim Delpassand, Stanley Garbus, Andrew Hendifar, Timothy Hobday, Matthew Kulke, Larry Kvols, David Metz, Erik Mittra, Michael Morse, Meike Schipper, Jonathan Strosberg, Edward Wolin, James Yao.

Funded by Advanced Accelerator Applications; ClinicalTrials.gov number NCT01578239; EudraCT number 2011-005049-11.

Supplementary Table S1. Demographic and Baseline Clinical Characteristics of the Patients at Enrollment (Full Analysis Set)

Characteristic	^{177}Lu-DOTATATE (N = 116)	Octreotide LAR 60 mg (N = 113)
Gender— no. (%)		
Female	53 (46)	60 (53)
Male	63 (54)	53 (47)
Mean age (SD) — yr	63 (±9)	64 (±10)
Mean BMI (±SD) — kg/m^2	25 (±5)	26 (±7)
Continent of origin— no. (%)		
USA	66 (57)	69 (61)
EU	50 (43)	44 (39)
Median time since diagnosis — yr	3.8	4.8
Mean KPS (SD)	88.6 (±9.32)	88.0 (±9.56)
Primary tumor site — no. (%)		
Jejunum	6 (5)	9 (8)
Ileum	86 (74)	82 (73)
Small intestine	11 (9)	12 (11)
Appendix	1 (1)	2 (2)
Right colon	3 (3)	1 (1)
Midgut (not otherwise specified)	9 (8)	7 (6)
Site of metastasis — no. (%)		
Liver	97 (84)	94 (83)
Lymph nodes	77 (66)	65 (58)
Mesentery	17 (15)	8 (7)
Bone	13 (11)	12 (11)
Lungs	11 (9)	5 (4)
Peritoneum	7 (6)	10 (9)
Ovaries	1 (1)	9 (8)
Other	15 (13)	10 (9)

Ki67 index — no. (%)		
Grade 1/2	76/40 (66/35)	81/32 (72/28)
SRS, Krenning scale — no. (%)[†]		
Grade 2	11 (10)	12 (11)
Grade 3	34 (29)	34 (30)
Grade 4	71 (61)	67 (59)
Median chromogranin A (quartiles) — µg/l[$]	604 (247–2626)	648 (290 – 2674)
Median 5-HIAA (quartiles)[‡]— mg/24hr[$]	36 (17-126)	44 (21-92)
Median serum alkaline phosphatase (quartiles) — U/l[$]	99 (74-160)	106 (75-152)
Previous treatments—no. (%)*		
Surgery	93 (80)	93 (82)
Tumor resection	90 (78)	93 (82)
Tumor ablation	6 (5)	11 (10)
Targeted therapy**	19 (16)	17 (15)
Embolization[#]	18 (16)	13 (12)
Chemotherapy	11 (9)	14 (12)
Interferon	8 (7)	7 (6)
Angiogenesis inhibitor	6 (5)	2 (2)
Radiotherapy (external beam radiation)	4 (3)	6 (5)
PRRT	1 (1)	0 (0)
Investigational drug	1 (1)	1 (1)
^{131}I MIBG	0 (0)	2 (2)

5-HIAA denotes 5-hydroxyindoleacetic acid, BMI body mass index, PRRT peptide receptor radionuclide therapy, SD standard deviation, and SRS somatostatin receptor scintigraphy.

[†]Highest grade.

[‡]Available in 82 and 84 patients, in ^{177}Lu DOTATATE and Octreotide LAR 60 mg group, respectively

*Other than somatostatin analogs (100% at study entry, inclusion criteria)

**Includes everolimus, temsirolimus, sunitinib, imatinib, sorafenib, pazopanib, axitinib and gefitinib

[#]Includes chemo-embolization, radio-embolization and trans-arterial embolization

[$]Normal range: CgA, 19.4 to 98.1 µg/l; 5HIAA, 0 to 15 mg/24hrs; AP, 0 to 150 U/l.

Supplementary Table S2. ^{177}Lu-DOTATATE Exposure.*

Patients who completed treatment phase (N=103†)	no. (%)
Number of administrations	
4	79 (77)
3	6 (6)
2	12 (12)
1	5 (5)
0	1 (1)
All treated patients (N=111)	
No DMT	103 (93)
DMT	8 (7)

* DMT denotes dose-modifying toxicity.

† Excluding patients still under treatment (n=8) or no treatment (n = 5).

SAFETY ASSESSMENTS

In both arms, safety assessment was performed every 12±1 weeks from the randomization date. In the active arm, during ^{177}Lu-DOTATATE treatment phase, additional safety visits were conducted every 2 to 4 weeks approximately. All adverse events (AEs), whether or not spontaneously reported by the patient, were recorded starting from the signing of the informed consent form (ICF) until the last study-related visit. Furthermore, a Data Safety Monitoring Board evaluated patient safety throughout the study. An AE was defined as any untoward medical occurrence in a patient and which did not necessarily have a causal relationship with the study medication. AEs were reported from the time the ICF was signed onwards until the progression-free survival (PFS) primary endpoint occurred, or until Week 76 post randomization if the PFS primary endpoint had been reached, or until early termination.

A serious AE (SAE) was any untoward medical occurrence that at any dose:

- Resulted in death;
- Was life-threatening;
- Resulted in persistent or significant disability/incapacity;
- Resulted in congenital anomaly or birth defect;
- Required inpatient hospitalization or leads to prolongation of hospitalization, with the exception of elective preplanned hospitalizations.

If a patient became pregnant during treatment, this had to be reported to the Sponsor Safety Officer as if it were an SAE. According to protocol, during the long-term follow-up, only SAEs related to ^{177}Lu-DOTATATE had to be reported to the Sponsor Safety Officer. In general, the investigator was requested to indicate the probable cause of the specific SAE in the appropriate section(s) of the SAE Reporting Form. The National Cancer Institute Common Terminology for Adverse Events (Version 4.03) was used for determining the severity of AEs.

In addition to the above-defined SAE, a set of potential risks deserved special attention even if they do not fulfill any of the seriousness criteria. These non-serious AEs of special interest (AESIs) occurring in patients enrolled in the investigational arm (^{177}Lu-DOTATATE) had to be

reported to the clinical trial pharmacovigilance department for safety analysis any time they occurred after enrollment including long term follow-up. Owing to the drug mechanism of action, hematotoxicity, secondary hematologic malignancies, and nephrotoxicity and cardiovascular events were investigated as AESIs. As the AESIs were not intended as a specific category of AEs for analysis in the Statistical Analysis Plan, the AESI flags in the database were not fully reconciled. To account for possible AESI underreporting an additional post hoc analysis was also conducted to identify AESIs in the two arms among the AEs/SAEs and the laboratory data as follows:

- Hematotoxicity: all grade ≥2 thrombocytopenia or grade 3/4 anemia/leukopenia/ neutropenia events not present at baseline were extracted from the laboratory dataset, as well as all the treatment-emergent AEs/SAEs with the Preferred Term related to this toxicity category (different from thrombocytopenia, anemia, leukopenia, neutropenia, because already extracted from the laboratory data). Secondary hematologic malignancies: all the treatment-emergent AEs/SAEs with the Preferred Term related to this toxicity category.
- Nephrotoxicity: all the treatment-emergent AEs/SAEs with the Preferred Term related to this toxicity category.
- Cardiovascular events: all the treatment-emergent AEs/SAEs with the Preferred Term related to this toxicity category.

All AEs occurring during the study were to be followed up until resolved or judged to be no longer clinically significant, or until they became chronic to the extent that they could be fully characterized. An assessment had to be made at the last study-related visit for each patient.

Laboratory assessments required that blood samples were taken for hematology and blood chemistry, and a urine sample for urinalysis, as listed below. Laboratory assessments were performed at the investigational site, except for the evaluation of serum chromogranin A. At screening: all patients had screening laboratory assessments including hematology, blood chemistry, and urinalysis; the assessment could be combined with baseline evaluation if sampling was within 3 weeks (preferably 2 weeks in the ^{177}Lu-DOTATATE arm) before the first treatment date. If laboratory data were available from a date that was less than 2 weeks since the signature of the ICF, those data could be considered acceptable for the initial screening of the patient (as

acknowledged in the ICF), if the repetition of the same examinations was regarded as useless. During the study, in the ^{177}Lu-DOTATATE arm: within 2 weeks before and 4±1 weeks after each ^{177}Lu-DOTATATE treatment. In addition, for the second, third, and fourth ^{177}Lu-DOTATATE treatment, an additional laboratory assessment was performed on the same day or within 1 day before treatment. Blood tests performed 4 weeks after any treatment could not serve as baseline values for the next treatment. A washout period was required between treatments. Patients were not eligible for their next treatment until a minimum of 7 weeks had passed since the last administration of study drug (maximum 16 weeks). Throughout the study, laboratory assessments were performed every 12±1 weeks since the first treatment date (Week 0). In the octreotide LAR 60 mg arm: throughout the study laboratory assessments were performed 4 weeks after the first treatment, and every 12±1 weeks since the first treatment date (Week 0). In the event of a significant laboratory abnormality, or if clinical or laboratory evidence of toxicity occurred, the investigator collected additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient was closely followed until sufficient information was obtained to determine the cause or the value regressed. Appropriate remedial measures were taken and the response recorded. All safety laboratory results had to be evaluated by the investigator before administration of study medication. Any clinically relevant change from baseline onwards was recorded on the Adverse Event page of the electronic case report form (e-CRF), possibly with a single diagnosis encompassing all changes supporting the single diagnosis. Laboratory assessments included the following:

- Hematology: white blood cell (WBC) count with differential (i.e. lymphocytes, monocytes, neutrophils, eosinophils, basophils), platelets, hemoglobin, mean corpuscular volume, and hematocrit.
- Blood chemistry: blood urea nitrogen, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, sodium, potassium, lactate dehydrogenase, chromogranin A (centralized assessment), glycosylated hemoglobin, free thyroxine, calcium, fasting blood glucose, and creatinine clearance (calculated by the Cockroft-Gault formula).

- Urinalysis: red blood cells per high-power field, WBCs per high-power field, casts per low-power field, protein (dipstick test was accepted to assess protein), pregnancy test if applicable (the latter at baseline for women of childbearing potential and during ^{177}Lu-DOTATATE therapy within 7 days before each treatment; blood pregnancy test was accepted). 5-hydroxyindoleacetic acid had to be done on 24-hour urine collection only at eligibility or baseline visit, at Weeks 12, 24, 36, 48, 60, 72, or 76 (and following 3-monthly laboratory assessments until the analysis of the PFS primary endpoint and at 6-month follow-up visits).

Patients with uncontrolled congestive heart failure (New York Heart Association class II–IV) were not eligible. Patients with a history of congestive heart failure who did not violate the above exclusion criteria underwent an evaluation of their cardiac ejection fraction before baseline, preferably via gated equilibrium radionuclide ventriculography. The results from an earlier study (not exceeding 30 days) may have substituted the evaluation at the discretion of the investigator, if no clinical worsening was noted. It was recommended that the patient's measured cardiac ejection fraction was >40% before randomization.

Electrocardiograms (ECGs) were recorded at baseline, immediately after each ^{177}Lu-DOTATATE treatment procedure (following the completion of the ^{177}Lu-DOTATATE infusion), and at the end of study to measure the different ECG intervals (RR, PR, QRS, and a more extended QT evaluation according to International Conference on Harmonisation Guideline E14, and heart rate). ECGs were taken also in the octreotide LAR 60 mg arm at the same timepoints (before the octreotide LAR injection). Standard 12-lead ECG was the preferred option, but if not possible, a 3-lead ECG was acceptable. An ECG in triplicate (at least 5 minutes apart) was taken supine, after 5 minutes rest, and not immediately after a meal. The parameters were measured as a mean value of minimally 3 beats; the mean of each parameter had to be used for eCRF completion. The investigator/local cardiologist noted in the source documents (and in the e-CRF) whether the ECG was normal or abnormal, as well as the clinical relevance of abnormal ECGs results and the different ECG interval measurements, calculated as the mean value of three measurements for each parameter. Relevant abnormalities at baseline were recorded in the Medical History

page, while changes during the study were recorded on the Adverse Event page of the e-CRF.

Physical examinations were performed by the investigator or qualified designee. All body systems were examined and any relevant findings were documented in the source documents and e-CRF. Physical examinations should have included heart rate, blood pressure, and weight measurement (height was only measured at baseline). Blood pressure and pulse rate measurements were performed after the patient rested for 5 minutes. For each patient, all blood pressure recordings should have been made using the same type of instrument (i.e., manual blood pressure recording vs. automatic digital vital signs monitor) on the same arm. Significant findings that were present before baseline were recorded in the Medical History page, while changes during the study (including significant changes of the symptoms due to the underlying disease vs. baseline, as reported in the diary card) were recorded on the Adverse Event page of the e-CRF.

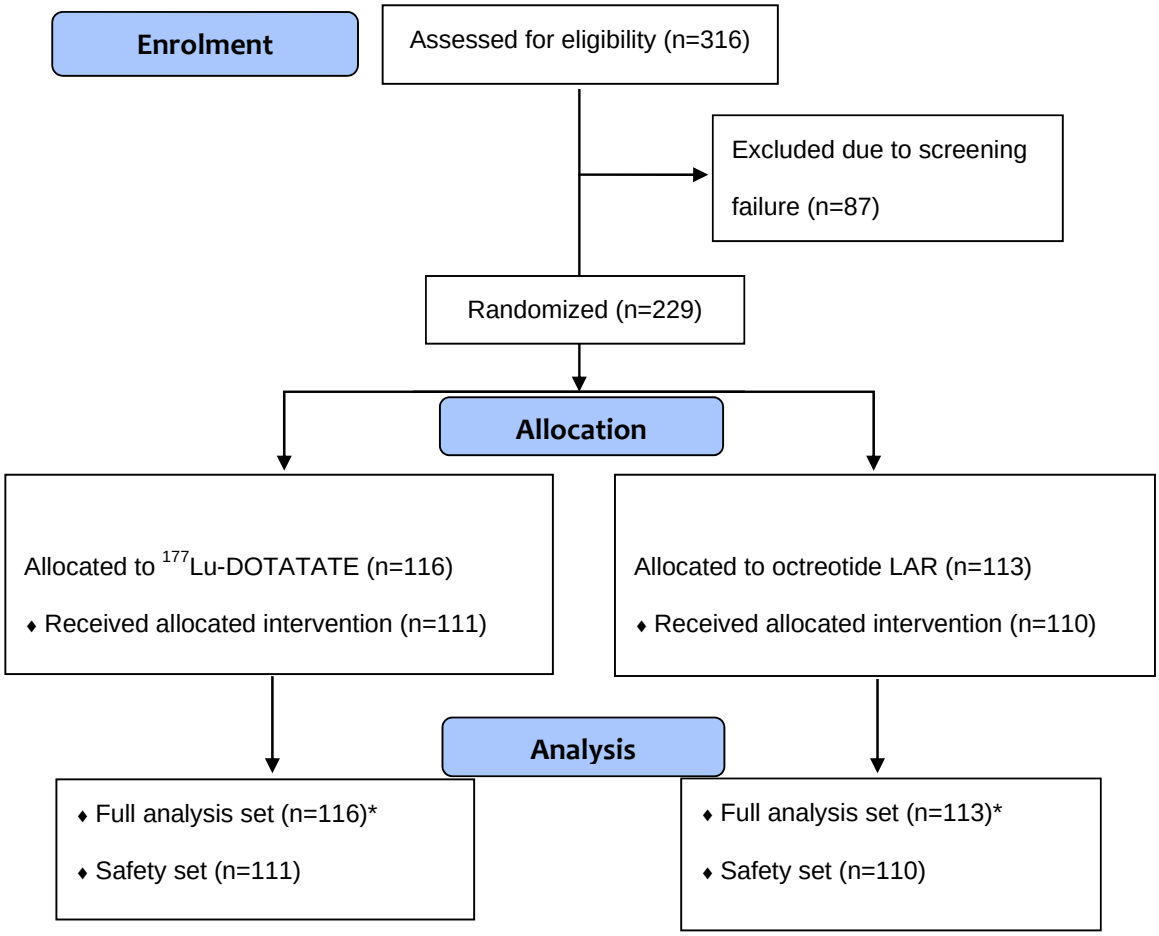
Karnofsky performance score forms had to be completed by a medical professional at each treatment and follow-up visit, and before any current clinical information was given to the patient.

The serious adverse reactions (SARs) reported by the investigators in the ^{177}Lu-DOTATATE arm were:

- One patient suffered from a serious episode of hepatic encephalopathy which required hospitalization but resolved without sequelae within 1 week. This SAR was related to the amino acids administration according to the investigator.
- One patient had mild thrombocytopenia which lasted for 28 days and was assessed as medically significant and related to ^{177}Lu-DOTATATE by the investigator. This SAR did not require any hospitalization or specific treatment/action.
- One patient had grade 3 thrombocytopenia assessed by the investigator as medically significant and related to ^{177}Lu-DOTATATE which required no specific action but was still ongoing at the time of database lock.

- One patient had grade 4 neutropenia assessed by the investigator as medically significant and related to ^{177}Lu-DOTATATE which required postponing next ^{177}Lu-DOTATATE infusion but resolved within 10 days.
- One patient suffered from an episode of syncope which was considered medically significant and related to amino acid infusion by the investigator. The SAR resolved spontaneously within few hours.
- One patient had an increase in creatinine levels (to 105 µmol/L, which was not abnormal per se, but was a 32% increase compared to baseline) which lasted for 27 days and required postponing the subsequent cycle of ^{177}Lu-DOTATATE. This SAR was assessed as related to ^{177}Lu-DOTATATE and improved at database lock.
- One patient had a moderate increase in creatinine (up to 1.95 mg/dL) and decrease of creatinine clearance (down to 36 ml/min; baseline 76 ml/min) which were seen as medically significant and related to ^{177}Lu-DOTATATE by the investigator, and necessitated postponing the next investigational product administration. These SARs resolved without sequelae within about 6 months.
- One patient suffered from severe abdominal ascites, related to ^{177}Lu-DOTATATE according to the investigator, which lasted for several months and necessitated therapeutic paracentesis procedures and one TIPS procedure before resolving without sequelae.
- One patient suffered from mild proteinuria and renal dysfunction which were assessed as medically significant and related to ^{177}Lu-DOTATATE by the investigator. This SAR did not require any hospitalization or specific treatment/action, but was still ongoing at the time of database lock.
- One patient suffered from significant dehydration related to ^{177}Lu-DOTATATE according to the investigator, which necessitated hospitalization but resolved within 3 days.

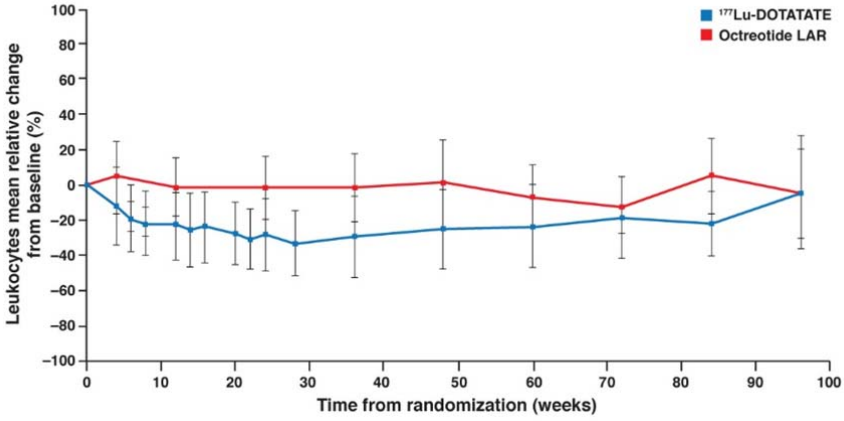
Supplementary Figure 1



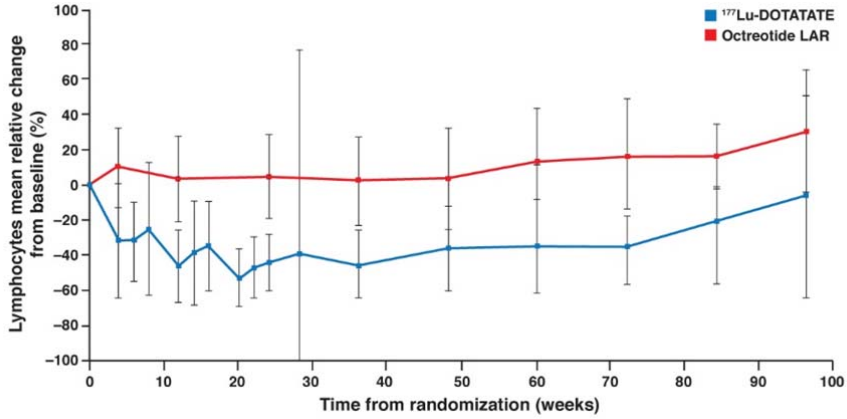
*At the time of the analysis cutoff date (July 2015), 15 patients in the 177Lu-DOTATATE arm and 13 patients in the Octreotide LAR arm had no follow-up scans

Supplementary Figure 2 – Hematological parameters mean relative change from baseline evolution over time (Error bars indicate standard deviations of the mean)

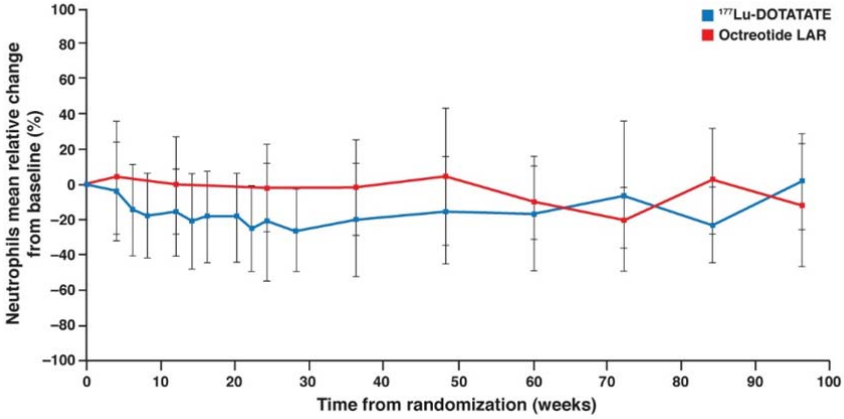
2a.



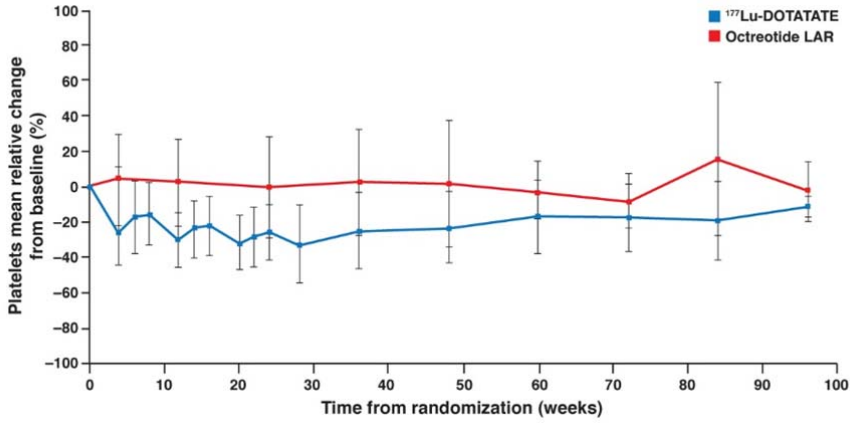
2b.



2c.



2d.



Supplementary Figure 3